Clinical trial results:
Multicenter, International, Double-blind, Two-Arm, Randomized, Placebo-controlled Phase II Trial of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing ILD

Summary

EudraCT number	2016-002744-17
Trial protocol	ES DK CZ DE PL PT GR BE GB IT
Global end of trial date	10 January 2020

Results information

Result version number	v2 (current)
This version publication date	07 January 2021
First version publication date	03 December 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MA39189

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03099187
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124., Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the effect of pirfenidone versus (vs.) placebo on lung function parameters.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	253
EEA total number of subjects	179

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	165
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 253 subjects were randomized at 65 study centers) in Australia, Europe, the Middle East, and North America. Subjects who were withdrawn from the trial were not replaced.

Pre-assignment

Screening details:

Subjects were requested to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period.

Period 1

Period 1 title	Double-Blind Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pirfenidone

Arm description:

Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pirfenidone was administered at a daily dose of 2403 mg orally in the form of three 267 mg capsules (801 mg) three times daily with food.

Arm title	Placebo

Arm description:

Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Arm type	Placebo
Investigational medicinal product name	Pirfenidone matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pirfenisone matching placebo was administered orally in the form of hard capsules three times daily.

Number of subjects in period 1	Pirfenidone	Placebo
Started	127	126
Completed	94	110
Not completed	33	16
Adverse event, serious fatal	1	3
Randomization error	-	2
Physician decision	2	1
Consent withdrawn by subject	9	4
Disease progression	-	1
Adverse event, non-fatal	19	1
Lung transplantation	-	1
Non-compliance with study drug	-	2
Non-compliance with Protocol procedure	1	1
Lack of efficacy	1	-

Period 2

Period 2 title	12-month Safety Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Open-Label Treatment (Pirfenidone)

Arm description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Arm type	Experimental
Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pirfenidone was administered at a daily dose of 2403 mg orally in the form of three 267 mg capsules (801 mg) three times daily with food.

Arm title	Open-Label Treatment (Placebo)

Arm description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Arm type	Experimental
Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pirfenidone was administered at a daily dose of 2403 mg orally in the form of three 267 mg capsules (801 mg) three times daily with food.

Number of subjects in period 2	Open-Label Treatment (Pirfenidone)	Open-Label Treatment (Placebo)
Started	94	110
Completed	75	84
Not completed	19	26
Adverse event, serious fatal	7	9
Consent withdrawn by subject	3	2
Due to hospitalization	-	1
Adverse event, non-fatal	5	12
Symptomatic deterioration	1	1
Lung transplantation	2	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Pirfenidone
Reporting group description:	
Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.	

Reporting group values	Pirfenidone	Placebo	Total
Number of subjects	127	126	253
Age categorical Units: Subjects			
Adults (18-64 years)	43	42	85
From 65-84 years	82	83	165
85 years and over	2	1	3
Age Continuous Units: Years			
arithmetic mean	68.0	67.7	
standard deviation	± 10.1	± 9.2	-
Sex: Female, Male Units: Subjects			
Female	57	57	114
Male	70	69	139
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	7	9	16
Not Hispanic or Latino	115	112	227
Not reported	5	5	10
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaskan Native	1	0	1
Asian	5	0	5
Black or African American	1	2	3
Other	0	1	1
White	120	123	243

End points

End points reporting groups

Reporting group title	Pirfenidone

Reporting group description:

Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Reporting group title	Open-Label Treatment (Pirfenidone)

Reporting group description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Reporting group title	Open-Label Treatment (Placebo)

Reporting group description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Subject analysis set title	Intent-toTreat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

Subject analysis set title	Safety Follow-Up Population
Subject analysis set type	Safety analysis

Subject analysis set description:

For the 12-month safety follow-up period, the safety follow-up population was defined as all subjects who received at least one dose of pirfenidone after the end of randomized treatment plus 28 days. Safety analyses for the 12-month follow-up period were performed from the date of the first pirfenidone drug intake during the safety follow-up period up to the study completion/discontinuation visit.

Primary: Rate of Decline in Forced Vital Capacity (FVC) Over the 24-week Double-blind Treatment Period

End point title	Rate of Decline in Forced Vital Capacity (FVC) Over the 24-week Double-blind Treatment Period

End point description:

Rate of decline in FVC was measured in mL by daily handheld spirometer. The analyses were repeated due to an additional independent review of the home spirometry data.

End point type	Primary

End point timeframe:

Up to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[1]	123[2]		
Units: milliliter (mL)				
arithmetic mean (confidence interval 95%)				
Primary Analysis in 2019	-17.9 (-311.7 to 275.9)	116.6 (-451.9 to 685.2)		
Final Analysis in 2020	-90.3 (-157.0 to -23.7)	125.6 (-458.4 to 709.6)		

Notes:

[1] - 116 subject data analyzed in 2020.

[2] - 116 subject data analyzed in 2020.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019

Statistical analysis description:

Mean FVC decline comparison between treatment groups using a Student's t-test with a two-sided significance level of 0.05

Comparison groups	Placebo v Pirfenidone
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6777 [3]
Method	t-test, 2-sided
Parameter estimate	Difference in Group Means
Point estimate	-134.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-772.4
upper limit	503.3

Notes:

[3] - p-value is not adjusted for multiplicity and is provided for descriptive purpose only

Statistical analysis title	Final analysis in 2020

Statistical analysis description:

Mean FVC decline comparison between treatment groups using a Student's t-test with a two-sided significance level of 0.05

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4682 [4]
Method	Student's t-test
Parameter estimate	Difference in Group Means
Point estimate	-216

Confidence interval	
level	95 %
sides	2-sided
lower limit	-803.6
upper limit	317.7

Notes:

[4] - p-value was not adjusted for multiplicity and is provided for descriptive purpose only

Secondary: Change in Percent Predicted FVC

End point title	Change in Percent Predicted FVC

End point description:

FVC was measured in liter (L) by spirometry. The analyses were repeated due to additional data cleaning activities that were not conducted during the primary analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[5]	126[6]		
Units: Percent predicted (%)				
arithmetic mean (standard deviation)				
Baseline (Day 1)	73.95 (± 18.815)	73.95 (± 19.974)		
Week 4	74.04 (± 19.009)	74.55 (± 21.223)		
Week 8	73.98 (± 19.324)	73.50 (± 20.168)		
Week 12	73.96 (± 19.493)	73.91 (± 20.856)		
Week 16	74.56 (± 20.299)	72.65 (± 22.479)		
Week 20	73.94 (± 21.000)	71.99 (± 21.673)		
Week 24	72.95 (± 20.819)	73.55 (± 22.383)		

Notes:

[5] - Number of subjects analysed was different at each time point; only collected data were analysed.

[6] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0383
Method	rank ANCOVA

Statistical analysis title	Final analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0239
Method	rank ANCOVA

Secondary: Change in FVC

End point title	Change in FVC

End point description:

FVC was measured in liter (L) by spirometry. The analyses were repeated due to additional data cleaning activities that were not conducted during the primary analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[7]	126[8]		
Units: Litre (L)				
arithmetic mean (standard deviation)				
Baseline	2.36 (± 0.793)	2.38 (± 0.747)		
Week 4	2.37 (± 0.818)	2.37 (± 0.786)		
Week 8	2.37 (± 0.822)	2.36 (± 0.816)		
Week 12	2.37 (± 0.820)	2.35 (± 0.773)		
Week 16	2.41 (± 0.860)	2.31 (± 0.782)		
Week 20	2.40 (± 0.866)	2.30 (± 0.796)		
Week 24	2.37 (± 0.863)	2.34 (± 0.773)		

Notes:

[7] - Number of subjects analysed was different at each time point; only collected data were analysed.

[8] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 [9]
Method	Student's t-test
Parameter estimate	Overall Mean Difference
Point estimate	95.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.9
upper limit	154.6

Notes:

[9] - p-value was not adjusted for multiplicity and is provided for descriptive purpose only.

Statistical analysis title	Final analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096 [10]
Method	Student's t-test
Parameter estimate	Overall Mean Difference
Point estimate	84.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.7
upper limit	147.8

Notes:

[10] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Secondary: Categorical Change in FVC of >5%

End point title	Categorical Change in FVC of >5%

End point description:

Categorical change in FVC was measured both by daily spirometry as well as by spirometry during clinical visits. Only the site spirometry data were used as the daily spirometry data were not normally distributed. The analyses were repeated due to additional data cleaning activities that were not conducted during the primary analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Number of Subjects				
Primary Analysis in 2019	47	74		
Updated Analysis in 2020	47	73		

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.69

Notes:

[11] - p-values was not adjusted for multiplicity and was provided for descriptive purpose only

Statistical analysis title	Final analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0009 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.71

Notes:

[12] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Secondary: Categorical Change in FVC of >10%

End point title	Categorical Change in FVC of >10%

End point description:

Categorical change in FVC was measured both by daily spirometry as well as by spirometry during clinical visits. Only the site spirometry data were used as the daily spirometry data were not normally

distributed. The analyses were repeated due to additional data cleaning activities that were not conducted during the primary analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Number of Subjects				
Primary Analysis in 2019	18	34		
Updated Analysis in 2020	18	33		

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.84

Notes:

[13] - p-values was not adjusted for multiplicity and was provided for descriptive purpose only

Statistical analysis title	Final analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0168 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.88

Notes:

[14] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Secondary: Change in Percent Predicted Diffusing Capacity of the Lung for Carbon Monoxide (DLco)

End point title	Change in Percent Predicted Diffusing Capacity of the Lung for Carbon Monoxide (DLco)

End point description:

The DLco is a pulmonary function test that measures the capacity for the lung to carry out gas exchange between the inhaled breath and the pulmonary capillary blood vessels and the DLco %-predicted represents the DLco expressed as a percentage of the expected normal valued based on the participant's age, height, gender and ethnicity.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[15]	125[16]		
Units: Percent Predicted				
arithmetic mean (standard deviation)				
Baseline (Day 1)	46.19 (± 12.403)	49.57 (± 13.931)		
Change from Baseline at Week 12 (Primary Analysis)	-0.52 (± 6.193)	-0.56 (± 8.807)		
Change from Baseline at Week 24 (Primary Analysis)	-0.65 (± 7.113)	-2.47 (± 8.833)		
Change from Baseline at Week 12 (Final Analysis)	-0.52 (± 6.193)	-0.89 (± 9.407)		
Change from Baseline at Week 24 (Final Analysis)	-0.65 (± 7.113)	-2.48 (± 8.893)		

Notes:

[15] - Number of subjects analysed was different at each time point; only collected data were analysed.

[16] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0874 [17]
Method	rank ANCOVA

Notes:

[17] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1191 [18]
Method	rank ANCOVA

Notes:

[18] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Secondary: Change in 6-minute Walk Distance (6MWD)

End point title	Change in 6-minute Walk Distance (6MWD)

End point description:

Comparison of 6-minute walk distance before beginning and after completing study therapy.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[19]	126[20]		
Units: meter (m)				
arithmetic mean (standard deviation)				
Baseline	391.6 (± 114.93)	394.0 (± 108.09)		
Change from Baseline at Week 12	-14.8 (± 66.23)	-7.7 (± 57.60)		
Change from Baseline at Week 24	-2.0 (± 68.11)	-26.7 (± 79.32)		

Notes:

[19] - Number of subjects analysed was different at each time point; only collected data were analysed.

[20] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395 [21]
Method	rank ANCOVA

Notes:

[21] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0299 [22]
Method	rank ANCOVA

Notes:

[22] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Secondary: Change in University of California, San Diego-Shortness of Breath Questionnaire Score

End point title	Change in University of California, San Diego-Shortness of Breath Questionnaire Score

End point description:

University of California, San Diego Shortness of Breath Questionnaire (SOBQ) consists of 24-item on a scale of 0 to 5 with 0=not at all and 5=maximal or unable to do because of breathlessness. The total scores were calculated by summation of the 24 items scores and transformed into 0-100, with 0= poor quality of life , and 100= excellent quality of life.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113[23]	114[24]		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Baseline	44.17 (± 25.204)	48.89 (± 23.441)		
Change from Baseline at Week 12	1.47 (± 19.707)	2.24 (± 18.617)		
Change from Baseline at Week 24	5.21 (± 18.701)	5.30 (± 22.078)		

Notes:

[23] - Number of subjects analysed was different at each time point; only collected data were analysed.

[24] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7788
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	5

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8289 [25]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	5

Notes:

[25] - Analysis of Covariance Changes from baseline to week 24 or early discontinuation visit are compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate

Secondary: Change in Score in Leicester Cough Questionnaire Score

End point title	Change in Score in Leicester Cough Questionnaire Score

End point description:

The Leicester Cough Questionnaire is a subject-reported questionnaire evaluating the impact of cough on quality of life. The questionnaire comprises 19 items. Each item assesses symptoms, or the impact of symptoms, over the last 2 weeks on a seven-point Likert scale. Scores in three domains (physical, psychological and social) were calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) was also calculated by adding the domain scores together. Higher scores indicate better quality of life.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[26]	125[27]		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Baseline	16.13 (± 3.711)	15.15 (± 3.928)		
Change from Baseline at Week 12 (Primary Analysis)	0.35 (± 2.903)	-0.23 (± 3.654)		
Change from Baseline at Week 24 (Primary Analysis	0.36 (± 2.889)	0.04 (± 3.702)		

Change from Baseline at Week 12 (Final Analysis)	0.35 (± 2.903)	-0.23 (± 3.654)		
Change from Baseline at Week 24 (Final Analysis)	0.35 (± 2.884)	0.04 (± 3.702)		

Notes:

[26] - Number of subjects analysed was different at each time point; only collected data were analysed.

[27] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1872 [28]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	1.04

Notes:

[28] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2019 [29]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	1.02

Notes:

[29] - Analysis of Covariance Changes from baseline to week 24 or early discontinuation visit are compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

Secondary: Change in Cough Visual Analog Scale (VAS) Score

End point title	Change in Cough Visual Analog Scale (VAS) Score

End point description:

Cough VAS are 100-mm linear scales on which subjects indicate the severity of their cough; 0 mm represents no cough and 100 mm the worst cough ever.

End point type	Secondary

End point timeframe:
Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[30]	125[31]		
Units: millimeter (mm)				
arithmetic mean (standard deviation)				
Baseline	35.60 (± 27.497)	37.18 (± 26.270)		
Change from Baseline at Week 12	-4.33 (± 20.017)	3.32 (± 26.429)		
Change from Baseline at Week 24	-2.52 (± 26.720)	0.78 (± 30.121)		

Notes:
[30] - Number of subjects analysed was different at each time point; only collected data were analysed.
[31] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2995
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	4

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3372 [32]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	4

Notes:

[32] - Analysis of Covariance Changes from baseline to week 24 or early discontinuation visit are compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

Secondary: Change in Total and Sub-scores of the Saint George's Respiratory Questionnaire (SGRQ)

End point title	Change in Total and Sub-scores of the Saint George's Respiratory Questionnaire (SGRQ)

End point description:

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in subjects with diseases of airways obstruction. Three component scores are: Symptoms (respiratory symptoms and severity); Activity (activities that cause or are limited by breathlessness); Impacts (social functioning and psychological disturbances due to airway disease). Each component sub-scores are calculated from the summed weights for the positive responses to questions. Total score summaries the impact of disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status. It is calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[33]	126[34]		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Symptoms sub-score - Baseline	49.28 (± 21.687)	53.10 (± 21.450)		
Symptoms sub-score - Week 12	-2.60 (± 19.173)	0.86 (± 16.212)		
Symptoms sub-score - Week 24	-1.69 (± 19.186)	-0.66 (± 15.407)		
Activities sub-score - Baseline	63.93 (± 20.388)	66.96 (± 18.615)		
Activities sub-score - Week 12	1.17 (± 13.376)	1.13 (± 13.704)		
Activities sub-score - Week 24	1.25 (± 14.629)	2.22 (± 13.110)		
Impacts sub-score - Baseline	37.12 (± 20.484)	41.47 (± 20.520)		
Impacts sub-score - Week 12	0.29 (± 16.826)	0.33 (± 13.888)		
Impacts sub-score - Week 24	-0.18 (± 13.884)	1.07 (± 17.539)		
Total score - Baseline	47.37 (± 18.465)	51.46 (± 17.699)		
Total score - Week 12	-0.17 (± 13.633)	0.53 (± 11.724)		

Total score - Week 24	0.05 (± 12.549)	0.85 (± 13.383)		

Notes:

[33] - Number of subjects analysed was different at each time point; only collected data were analysed.

[34] - Number of subjects analysed was different at each time point; only collected data were analysed.

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	1.38

Statistical analysis title	Final Analysis in 2020
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1851 [35]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann Median Difference
Point estimate	-1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	1.55

Notes:

[35] - Analysis of Covariance Changes from baseline to week 24 or early discontinuation visit are compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

Secondary: Number of Subjects with Non-elective Hospitalization, Both Respiratory and all Cause

End point title	Number of Subjects with Non-elective Hospitalization, Both Respiratory and all Cause

End point description:

Subjects with non-elective hospitalization are reported.

End point type	Secondary

End point timeframe:
Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Number of Subjects				
All-cause hospitalization	16	13		
Respiratory-related hospitalization	5	5		

Statistical analyses

Statistical analysis title	All-cause non-elective hospitalization.

Statistical analysis description:

Primary Analysis in 2019. Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5922
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.49

Statistical analysis title	Respiratory non-elective hospitalization.

Statistical analysis description:

Primary Analysis in 2019. Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	2.83

Statistical analysis title	All-cause non-elective hospitalization.

Statistical analysis description:

Final Analysis in 2020. Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4613
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.73

Statistical analysis title	Respiratory non-elective hospitalization.

Statistical analysis description:

Final Analysis in 2020. Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9523
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.59

Secondary: Percentage of Subjects with Investigator-reported Acute Exacerbations

End point title	Percentage of Subjects with Investigator-reported Acute Exacerbations

End point description:

Percentage of subjects with acute exacerbation are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Percentage of Subjects				
number (not applicable)	3.9	5.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Investigator-reported Acute Exacerbations

End point title	Time to First Investigator-reported Acute Exacerbations

End point description:

Time to first investigator reported acute exacerbations from start of treatment are reported. 9999=not estimable; The end point could not be analysed due to the limited number of events.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7871
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	2.78

Secondary: Progression-free Survival (PFS) defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD

End point title	Progression-free Survival (PFS) defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD

End point description:

PFS is defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD, or death. 9999=not estimable

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Week				
median (confidence interval 95%)	25.14 (24.14 to 9999)	24.71 (24.14 to 9999)		

Statistical analyses

Statistical analysis title	Primary Analysis in 2019

Statistical analysis description:

Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.366
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.24

Statistical analysis title	Final Analysis in 2020
Statistical analysis description:	
Log-rank tests based on the time to the first event are to compare the two treatment arms.	
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4173
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.26

Secondary: PFS defined as the time to the first occurrence of a >10% relative decline in percent predicted FVC, non-elective respiratory hospitalization, or death

End point title	PFS defined as the time to the first occurrence of a >10% relative decline in percent predicted FVC, non-elective respiratory hospitalization, or death
End point description:	
PFS is defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, non-elective respiratory hospitalization, or death. 9999=not estimable	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Week 24	

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	126		
Units: Week				
median (confidence interval 95%)	9999 (24.86 to 9999)	9999 (24.14 to 9999)		

Statistical analyses

Statistical analysis title	Primary Analysis in 2019
Statistical analysis description: Log-rank tests based on the time to the first event are to compare the two treatment arms.	
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2726
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.2

Statistical analysis title	Final Analysis in 2020
Statistical analysis description: Log-rank tests based on the time to the first event are to compare the two treatment arms.	
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3386
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.24

Secondary: Time to Death From any Cause

End point title	Time to Death From any Cause

End point description:

Time to first documented death from start of treatment is reported. 9999=not estimable

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[36]	126[37]		
Units: Week				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[36] - The end point could not be analysed due to the limited number of events.

[37] - The end point could not be analysed due to the limited number of events

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9969
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	16.08

Secondary: Time to Death from Respiratory Diseases

End point title	Time to Death from Respiratory Diseases

End point description:

Time to first documented death due to respiratory diseases from start of treatment will be reported. 9999=not estimable

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[38]	126[39]		
Units: Week				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[38] - The end point could not be analysed due to the limited number of events

[39] - The end point could not be analysed due to the limited number of events

Statistical analyses

Statistical analysis title	Superiority

Statistical analysis description:

Log-rank tests based on the time to the first event are to compare the two treatment arms.

Comparison groups	Pirfenidone v Placebo
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3231
Method	Logrank

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124[40]		
Units: Subjects	120	101		

Notes:

[40] - Two subjects did not receive treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Dose Reductions and Treatment Interruptions during the Double-Blind Period

End point title	Number of Subjects With Dose Reductions and Treatment Interruptions during the Double-Blind Period

End point description:

Number of subjects with dose reduction and treatment interruptions are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

End point type	Secondary

End point timeframe:

From administration of the first dose of study drug to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124		
Units: Number of Subjects				
Subjects with at least one dose modification	51	34		
Subjects with at least one dose interruption	40	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Dose Reductions and Treatment Interruptions during the 12-month Safety Follow-up

End point title	Number of Subjects With Dose Reductions and Treatment Interruptions during the 12-month Safety Follow-up

End point description:

Number of subjects with dose reduction and treatment interruptions are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

End point type	Secondary

End point timeframe:

From the Follow-up Visit at Week 28 through the follow-up period of 12 Months

End point values	Open-Label Treatment (Pirfenidone)	Open-Label Treatment (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	110		
Units: Number of Subjects				
number (not applicable)				
Subjects with at least one dose modification	41	60		
Subjects with at least one dose interruption	24	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations during the Double-Blind Period

End point title	Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations during the Double-Blind Period

End point description:

Number of subjects withdrawn from trial treatment or trial discontinuations are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Pirfenidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124[41]		
Units: Number of Subjects	25	12		

Notes:

[41] - Two subjects did not receive treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations during the 12-month Safety Follow-up

End point title	Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations during the 12-month Safety Follow-up

End point description:

Number of subjects withdrawn from trial treatment or trial discontinuations are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

End point type	Secondary

End point timeframe:

From the Follow-up Visit at Week 28 through the follow-up period of 12 Months

End point values	Open-Label Treatment (Pirfenidone)	Open-Label Treatment (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	110		
Units: Number of Subjects				
number (not applicable)	19	26		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) to Week 28 in the double-blind period From the Follow-up Visit at Week 28 through the follow-up period of 12 Months in the open-label treatment period

Adverse event reporting additional description:

The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Pirfenidone

Reporting group description:

Participants received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

Reporting group title	Open-Label Treatment (Pirfenidone)

Reporting group description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Reporting group title	Open-Label Treatment (Placebo)

Reporting group description:

After subjects completed the double-blind treatment period and the follow-up visit at Week 28, they were offered the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Serious adverse events	Pirfenidone	Placebo	Open-Label Treatment (Pirfenidone)
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 127 (14.17%)	20 / 124 (16.13%)	26 / 94 (27.66%)
number of deaths (all causes)	4	7	7
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Lung transplant rejection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 127 (0.79%)	2 / 124 (1.61%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary fibrosis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pleuritic pain			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			

subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Product issues			
Device occlusion			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus test positive			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	3 / 94 (3.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericarditis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Presyncope			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 127 (0.79%)	3 / 124 (2.42%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia influenzal			

subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxocariasis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster pneumonia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label Treatment (Placebo)		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 110 (24.55%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Lung transplant rejection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	3 / 110 (2.73%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Respiratory disorder				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	3 / 110 (2.73%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pleuritic pain				

subjects affected / exposed	3 / 110 (2.73%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Product issues			
Device occlusion			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza A virus test positive			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Spinal compression fracture				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nephrolithiasis				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	4 / 110 (3.64%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 110 (5.45%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 2			

Respiratory tract infection				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection bacterial				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia influenzal			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia viral			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxocariasis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella zoster pneumonia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varicella zoster virus infection			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pirfenidone	Placebo	Open-Label Treatment (Pirfenidone)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 127 (84.25%)	81 / 124 (65.32%)	64 / 94 (68.09%)
Investigations			
Weight decreased			
subjects affected / exposed	11 / 127 (8.66%)	6 / 124 (4.84%)	2 / 94 (2.13%)
occurrences (all)	11	6	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 127 (8.66%)	13 / 124 (10.48%)	4 / 94 (4.26%)
occurrences (all)	13	14	4
Headache			
subjects affected / exposed	13 / 127 (10.24%)	4 / 124 (3.23%)	3 / 94 (3.19%)
occurrences (all)	19	5	3
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	21 / 127 (16.54%)	19 / 124 (15.32%)	5 / 94 (5.32%)
occurrences (all)	22	20	5
Pyrexia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 127 (5.51%)	4 / 124 (3.23%)	6 / 94 (6.38%)
occurrences (all)	7	4	6
Diarrhoea			
subjects affected / exposed	23 / 127 (18.11%)	23 / 124 (18.55%)	9 / 94 (9.57%)
occurrences (all)	27	24	16
Dyspepsia			
subjects affected / exposed	17 / 127 (13.39%)	7 / 124 (5.65%)	5 / 94 (5.32%)
occurrences (all)	21	7	5
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 127 (7.87%)	6 / 124 (4.84%)	7 / 94 (7.45%)
occurrences (all)	10	7	8
Nausea			
subjects affected / exposed	40 / 127 (31.50%)	9 / 124 (7.26%)	15 / 94 (15.96%)
occurrences (all)	49	10	18
Vomiting			
subjects affected / exposed	14 / 127 (11.02%)	6 / 124 (4.84%)	4 / 94 (4.26%)
occurrences (all)	17	7	6
Abdominal pain			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	1 / 94 (1.06%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 127 (14.96%)	16 / 124 (12.90%)	10 / 94 (10.64%)
occurrences (all)	21	17	12
Dyspnoea			

subjects affected / exposed	14 / 127 (11.02%)	22 / 124 (17.74%)	9 / 94 (9.57%)
occurrences (all)	16	25	10
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	8 / 127 (6.30%)	0 / 124 (0.00%)	2 / 94 (2.13%)
occurrences (all)	9	0	2
Rash			
subjects affected / exposed	9 / 127 (7.09%)	7 / 124 (5.65%)	8 / 94 (8.51%)
occurrences (all)	12	8	10
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 127 (5.51%)	0 / 124 (0.00%)	0 / 94 (0.00%)
occurrences (all)	7	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 127 (6.30%)	3 / 124 (2.42%)	0 / 94 (0.00%)
occurrences (all)	8	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 127 (7.87%)	3 / 124 (2.42%)	0 / 94 (0.00%)
occurrences (all)	11	3	0
Lower respiratory tract infection			
subjects affected / exposed	8 / 127 (6.30%)	13 / 124 (10.48%)	9 / 94 (9.57%)
occurrences (all)	10	16	12
Nasopharyngitis			
subjects affected / exposed	7 / 127 (5.51%)	6 / 124 (4.84%)	10 / 94 (10.64%)
occurrences (all)	8	9	11
Respiratory tract infection			
subjects affected / exposed	11 / 127 (8.66%)	5 / 124 (4.03%)	8 / 94 (8.51%)
occurrences (all)	11	7	9
Upper respiratory tract infection			
subjects affected / exposed	12 / 127 (9.45%)	9 / 124 (7.26%)	7 / 94 (7.45%)
occurrences (all)	15	10	9
Urinary tract infection			
subjects affected / exposed	0 / 127 (0.00%)	0 / 124 (0.00%)	7 / 94 (7.45%)
occurrences (all)	0	0	9

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	18 / 127 (14.17%) 22	11 / 124 (8.87%) 11	7 / 94 (7.45%) 8

Non-serious adverse events	Open-Label Treatment (Placebo)		
Total subjects affected by non-serious adverse events subjects affected / exposed	86 / 110 (78.18%)		
Investigations Weight decreased subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8 12 / 110 (10.91%) 12		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	12 / 110 (10.91%) 14 8 / 110 (7.27%) 9		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease	3 / 110 (2.73%) 5 15 / 110 (13.64%) 15 8 / 110 (7.27%) 9		

subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7		
Nausea subjects affected / exposed occurrences (all)	30 / 110 (27.27%) 39		
Vomiting subjects affected / exposed occurrences (all)	18 / 110 (16.36%) 25		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8		
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 12		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 9		
Dyspnoea subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8		
Skin and subcutaneous tissue disorders			
Photosensitivity reaction subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 12		
Rash subjects affected / exposed occurrences (all)	16 / 110 (14.55%) 19		
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		

Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	15		
Nasopharyngitis			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	11		
Respiratory tract infection			
subjects affected / exposed	4 / 110 (3.64%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 110 (11.82%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2017	1) Version included additional safety monitoring during the 12-month safety follow-up period, in accordance with the pirfenidone Investigator's Brochure (RO0220912) and the Summary of Product Characteristics (Esbriet). Increased safety monitoring included additional liver function and pregnancy tests initially at monthly visits during the first 6 months and approximately every 3 months, thereafter. Urine pregnancy tests would continue to be performed on a monthly basis. Relevant sections of the protocol including the Schedule of Assessments have been amended. 2) Guidance text for sections on inclusion and exclusion criteria was amended in order to provide more clear guidance as to when subjects must fulfil the eligibility criteria in order to participate in the trial since results for screening assessments may not all be available at the time of screening. 3) Inclusion criterion no. 11 was amended in order to correct the error in the classification of the acceptable methods of contraception. 4) Section on 'Trial Rationale and Benefit-Risk Assessment' was amended to provide further clarification that trial subjects are allowed to be treated with mycophenolate (MMF) regardless of which treatment arm they were randomized onto during the 24-week double-blind period and throughout the study.
03 March 2017	5) Section on 'Pirfenidone and Placebo' was amended in order to correct that no markings were made on the capsules. The list of printing ink ingredients was deleted. 6) Section on 'Method of Treatment Assignment and Unblinding' was amended in order to delete the sentence providing Investigators with the option of unblinding subjects for any other reason but safety. Unblinding could only occur for safety reasons. 6) Section on 'Electrocardiograms' was amended in order to revise the template text requiring for ECGs to be obtained prior to other trial procedures and not prior to treatment administration. This template text did not apply to this trial as there were no cardiac safety concerns with pirfenidone treatment or any justification for requiring ECGs to be obtained prior to any other study procedures. 7) The 'Cough Visual Analogue Scale' was amended in order to replace the previous scale with the actual scale and guidance text that would be provided to the subjects.
28 June 2018	Protocol was amended mainly in order to provide additional guidance on trial specific procedures. Changes to the protocol including the rationale for each change: 1) Synopsis (Target Population) and Protocol Section 4.1 (Patients) of the protocol were amended in order to provide guidance on conditions for allowing the rescreening of subjects. 2) Section 4.5.5 (FVC) was amended to provide guidance on when to use a short-acting bronchodilator prior to on-site spirometry for subjects who are routinely treated with such medication. 3) Sections 4.5.9 (Electrocardiograms) and 5.1.1.8 (Management of Increases in QT Interval) were amended to provide more clear guidance for ECGs and the management of increases in QT interval. 4) Section 4.5.10 (Patient-Reported Outcomes) was amended as the timing for the completion of the Patient-Reported Outcomes was independent of the administration time of the trial treatment. 5) Section 4.6.1 (Patient Discontinuation) was amended to include lung transplantation during the trial as a reason for subject discontinuation. 6) Schedule of Assessments was amended to reflect the changes made to the body of the protocol and also to provide further trial-specific guidance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported